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REVIEW ARTICLE

Survival of Patients With Untreated Breast Cancer

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Knowing the clinical prognosis of untreated breast cancer is useful in dealing with patients with neglected disease or in environments with poorly developed healthcare systems. This study analyzes historical survival data in two sets of untreated patients: (1) 250 patients followed until death (up to 12 years) for which autopsy results are available and (2) an amalgam of 1,022 patients from several papers. Data from nine published papers underwent actuarial analysis. Median survival time of the 250 patients followed to death was 2.7 years. Actuarial 5- and 10-year survival rates for these patients with untreated breast cancer was 18.4% and 3.6%, respectively. For the amalgamated 1,022 patients, median survival time was 2.3 years. Actuarial 5- and (partially fitted) 10-year survival rates for these patients with untreated breast cancer was 19.8% and 3.7%, respectively. Historical data of untreated breast cancer patients reveal a potential for long survival in some cases. The spectrum of clinical aggressiveness of breast cancer varies between virulence and chronic disease.
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KEY WORDS: breast neoplasms; untreated; actuarial analysis; historical data

INTRODUCTION

Most patients with new breast lesions or abnormal mammographic findings seek medical attention. In the United States, a minority do not seek medical attention, whether it is from lack of access to healthcare or a component of cultural bias and stigma. That fraction increases in other countries with less accessible systems of healthcare. There are scant recent data on outcomes in patients with neglected or untreated disease. This point is critical to healthcare in general: If we do not know the character of a disease in the absence of treatment, how can we be sure that our interventions are of benefit to the patient?

Because treatment cannot be ethically withheld in most cases, this baseline "natural history" is unlikely to emerge from modern studies. We propose that rigorous analysis of historical data from periods before effective therapies were available — or in large populations for whom such therapies were not used — can fill that void of knowledge.

This review was undertaken with that purpose. An often-quoted article by Bloom [1] provides crude survival data in a select cohort of 250 autopsied breast cancer patients at Middlesex Hospital between 1805 and 1933. In that article, crude summary data from other references are plotted. The current analysis rigorously collates the original data from those and other reports and subjects them to actuarial survival analysis.

The opinions or assertions contained herein are those of the authors and should not be construed as official or representing the views of the United States Navy or Department of Defense.

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TABLE I. References Used in Analysis of Untreated Breast Cancer

Reference, (%) autopsied	Year published	Years covered	n	Pathological diagnosis
Lazarus-Barlow and Leeming [3]	1924	1883–1922	243	
Wyard [4]	1925	1900–1924	273	
Greenwood [2]	1926		135	
Daland [5] (11%)	1927		100	11
Forber [6]	1931	1928–1929	64	
Nathanson and Welch [7]	1936	1912–1932	50	
Wade [8]	1946	1931–1941	26	
Phillips [9] (20%)	1959		230	46
Bloom et al. [10] (100%)	1962	1805–1933	250	

MATERIALS AND METHODS

A comprehensive search was made of MEDLINE using the descriptors breast neoplasms, natural.tw, untreated.tw, and history.tw. Review was made of retrieved material, as well as references and related material. Ten articles [1–10] were identified; they dealt with survival of breast cancer patients for whom no anti-tumor therapy was delivered. Particulars of these articles are listed in Table I. (Reference 10 is a precursor to reference 1 and contains more complete information on the data.) These studies vary in diagnostic rigor and mechanism of follow-up, but all provide crude survival data listed by years of follow-up. Although breast cancer therapy varied substantially in the interval between 1805 and 1941 (i.e., the years encompassed by the studies referenced), the studies are consistent in that no patient received potentially curative surgery or radiotherapy.

Collated crude survival data were analyzed using the method of Kaplan and Meier [11]. Overlap of data between studies was corrected using the following techniques:

1. Greenwood [2] reported otherwise unpublished data provided by Beatson, White, and Carter-Braine, in addition to some data previously reported by Lazarus-Barlow and Leeming [3] and Wyard [4]. Specifically regarding the latter authors, no data were provided in the earlier publications [3,4] regarding crude survival by date of follow-up.

2. Nathanson and Welch [7] added 50 patients to 50 who had previously been reported by Daland [5]. The later analysis was less well described than the earlier one and there was no mechanism to separate the two sets of data in the survival curve from Nathanson and Welch (their Fig. 4). Therefore, to avoid duplication of patients, no data were extracted from Nathanson and Welch [7] for analysis.

3. Phillips [9] collected 230 cases from cancer treatment centers in Canada, England, France, and the United States. Although no specific data from individual sites are discussed, comparison is made with Daland's data [5], and no other article reported on Canadian patients. We consider it acceptable to use Phillips' data [9] in its entirety.

4. Bloom et al. [10] reported some patients from Middlesex Hospital who were previously reported by Greenwood [2] and credited to Lazarus-Barlow and Leeming [3]. Bloom et al. [10] provide no breakdown for extraction of previously reported patients. Therefore, if we included both the 516 patients from Greenwood [2] and the 250 patients from Bloom et al. [10], an unknown number of patients would be counted twice. To avoid this, no data from the subsequent Bloom et al. report [10] were included in our actuarial analysis. However, because Bloom et al. [10] added a measure of rigor to their article by following patients until death and only reporting on autopsied patients, data from the Bloom et al. report [10] and from other sources [2–9] were analyzed separately.

There are potential hazards in too rigorously interpreting data from disparate sources, including absence of original data; uneven quality of reporting (especially from data over 100 years old); and potential bias in the selection of data. A careful review of the articles and their data was made prior to inclusion. Some reassurance as to quality is given by the similarity of median survival times, of year-by-year survival rates, and of parameters resulting from logarithmic regression model fits. An overlay of Figures 1 and 2 reveals that these factor are very similar.

The data from the Bloom et al. article [10] and the first 5 years of the amalgamated papers [2–9] were subjected to traditional epidemiological methods: life table and Kaplan-Meier analysis. Table II shows that some data sets are not carried past 5, 6, or 7 years and others report 10 or 15 years of survival numbers but omit some intervening data. To be able to carry the survival analysis to 10 years for the amalgamated data, estimates of the missing survival numbers were made. Logarithmic regression was used to assess the similarity of the various data sets. However, it was not used to estimate missing data because estimates of intervening survival numbers were sometimes less than observed final numbers. Due to the logarithmic nature of the decline in survival numbers, the

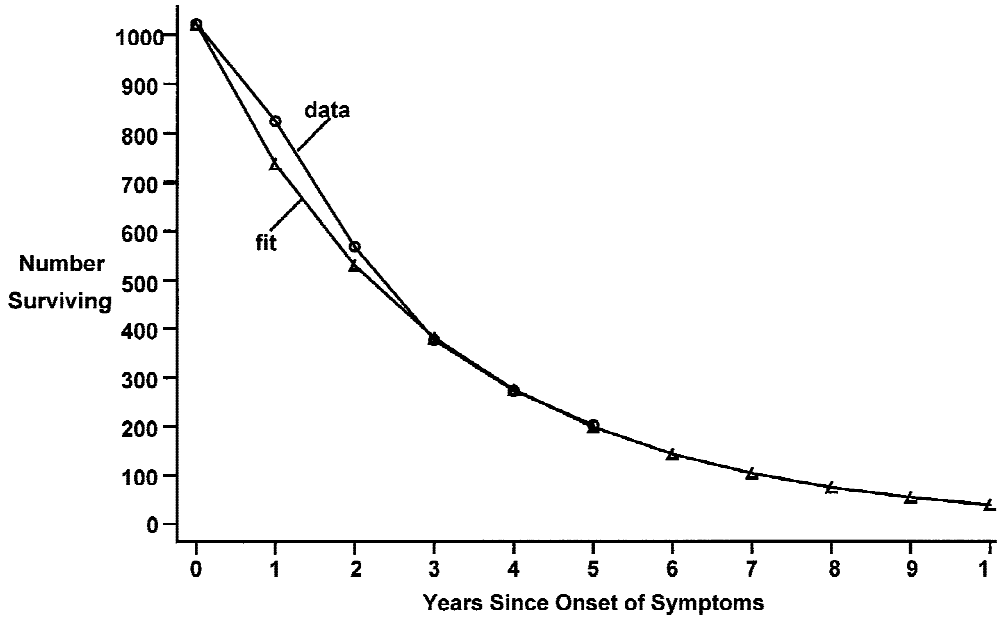

Fig. 1. Analysis of accuracy of survival data fit.

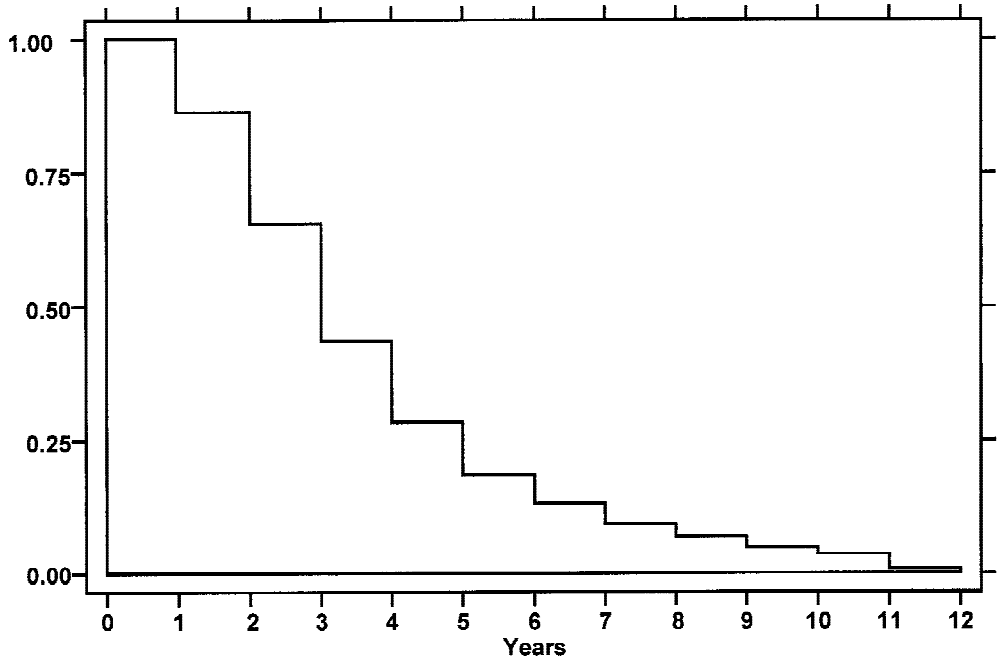

Fig. 2. Actuarial survival of 250 autopsied untreated breast cancer patients Data from Bloom et al. [10].

rate surviving was approximately constant. This constant was estimated as the mean of proportion surviving each year. A new set of survival number estimates was created for each data set by multiplying each year's survival by this constant to obtain the subsequent year's survival. The quality of this estimation procedure was evaluated by comparing logarithmic regression fits of the actual data and the estimated data. For all data sets, the coefficients of determination (R^2) were within 1% of each other and were 0.97–0.98 in value. For the amalgamated data, R^2 was 0.978 for the original data and 0.980 for the fit.

To perform the analysis, actual data were used when present; when absent, the estimated data were supplied. Figure 1 shows a comparison of the observed and fitted data for the amalgamated 1,022 patients.

RESULTS

Table II collates crude survival data for patients with untreated breast cancer from references [2–10]. Figure 2 shows a Kaplan-Meier survival curve for the data from Bloom et al. [10]. Median survival of these 250 patients followed to death and subsequently autopsied was 2.7 years. Actuarial 5- and 10-year survival rates for these

TABLE II. Survival Data From Onset of Symptoms of Breast Cancer

Reference	n	No. alive by end of follow-up year												Survival (months)	
		1	2	3	4	5	6	7	8	9	10	15	20	Mean	Median
Collected Data															
Lazarus-Barlow and Leeming [3]	243[a]	434	291	187	129	89	64	49						39.8	
Wyard [4]	273[a]													39.6	
Greenwood [2]	135[b]	107	69	37	26	16	4	11						33.9	
Daland [5]	100	79	59	40	30	22	14	9			5	0		40.5	30
Forber [6]	64[c]	51	34	28	23	20								39.3 vs 38.4	17.4[d]
	466[e]	Not specifically reported													50.7
Nathanson and Welch [7]	100[f]	Not specifically reported													
Wade [8]	26	17	9	5	3	3	2							32.6	
Phillips [9]	181	136	105	80	62	52					12			46.2	
Cumulative crude survival	1022	824	567	377	273	202									
Crude % survival		80.6	55.5	36.9	26.7	19.8									
Autopsy Data															
Bloom et al. [10]	250[g]	216	164	109	71	46	33	23	17	12	9	2	0	35.5	32.4
Crude % survival		86.4	65.6	43.6	28.4	18.4	13.2	9.2	6.8	4.8	3.6	0.8			

[a]Combined in reference 2, in (Table 4); no breakdown by author in that reference or earlier [3,4].
[b]Includes data reported by Beatson, White, and Carter-Braine. Obtained by subtracting Tables 4 from 5 in reference 2.
[c]Data from London.
[d]Author excluded 2 patients with 40–41 year survival.
[e]County Borough data.
[f]Includes data previously reported by Daland.
[g]Includes some autopsied patients reported by Lazarus-Barlow and Leeming (reported by Greenwood [2]).

patients was 18.4% and 3.6%, respectively, with two patients surviving to 12 years. Figure 3 shows a Kaplan-Meier survival curve for the amalgamated 1,022 patients from references [2–9], with missing data estimated by fitting techniques. Median survival time was 2.3 years. Actuarial 5- and 10-year survival rates were 19.8% and 3.7%, respectively.

DISCUSSION

Neglected breast cancer is a rare occurrence in most clinical practices and occurs infrequently in the United States. These data indicate what would be expected without treatment as a baseline against which the efficacy of treatment may be compared. Although it must be recognized that in none of these reports was selection of patients for therapy well described, some of the studies referenced here compared outcomes of patients with untreated disease with patients who underwent surgical or radiation therapy. Daland [5] described crude 7-year overall survival rates of 35.5% for 66 treated patients and 9% for 100 untreated patients. In an update, Nathanson and Welch [7] provided a graphical plot (their Fig. 5) with crude 7-year survival rates of 22% for 1,530 treated cases and 10% for 100 untreated cases. Wade [8] reported 5-year crude survival rates of 9.5% for 177 treated patients and 0% for 27 untreated patients. In this study, the treated cohort included patients who had both surgery and radiation therapy, as well as some who had radiation only.

Phillips [9] documented case-controls that showed that treatment contributed to statistically prolonged survival through only 7 years after the date of diagnosis, and was essentially not a significant factor when survival from date of onset of symptoms was used. Bloom et al. [10] reported on survival rates of treated and untreated patients. Their treated patients were compiled from 1936 to 1949; 84% of patients had surgical resection with or without radiation therapy and the remainder had radiation therapy alone. The untreated group was compiled from 1805 to 1933. In both groups, survival was measured from onset of symptoms. In the treatment group, crude survival rates were 55% at 5 years, 34% at 10 years, and 22% at 15 years. In the untreated group, the corresponding rates were 18%, 3.6%, and 0.8%, respectively.

Comparison with more current series further confirms that therapy improves survival. Treatment with local therapy (modified radical mastectomy or lumpectomy and radiation) will improve both local disease control and survival [12]. Because we now know that a significant portion of women with breast cancer have subclinical metastases and that this risk increases with nodal disease, chemotherapy and hormonal therapy have become standard treatment. The Early Breast Cancer Trialists' Collaborative Group [13] overviewed 400 randomized trials in over 220,000 women and clearly

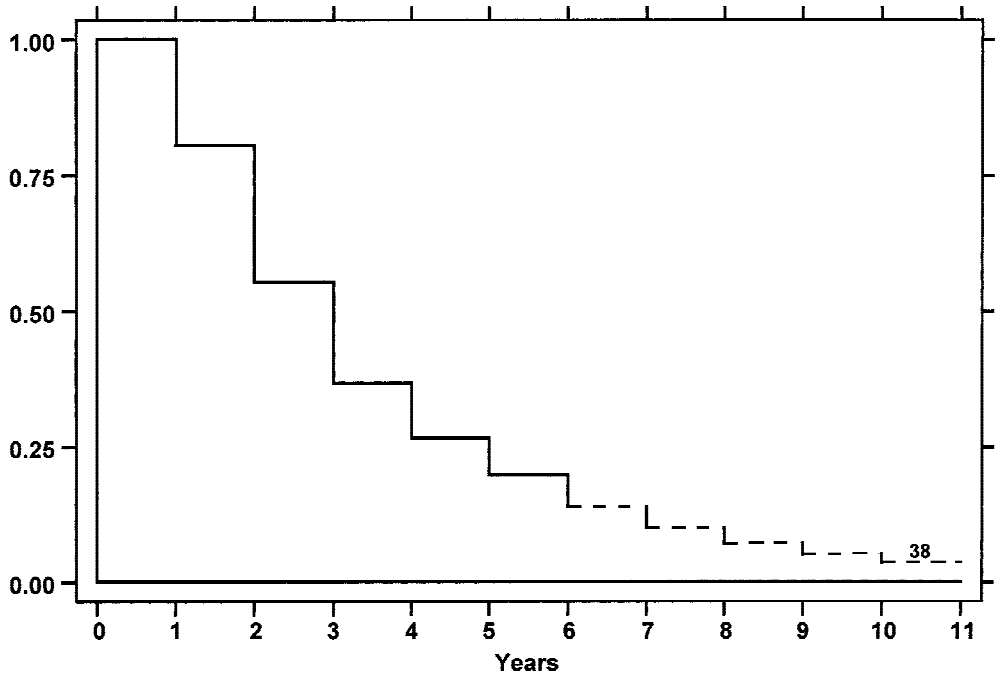

Fig. 3. Actuarial survival of 1,022 untreated breast cancer patients. Data data from several sources [2–6,8,9]. Dashed lines represent interpolated data (see text for details).

showed that both treatment with chemotherapy and hormonal therapy improved the natural history of breast cancer. Adjuvant combination chemotherapy will reduce the annual risk of death by about 20%. The overview also demonstrated the use of adjuvant tamoxifen therapy to significantly reduce the risks of recurrence and death in all age groups with receptor positive disease.

It must be noted that more separates the unfortunate patients analyzed herein from the present than mere time. Advances in stem cell factor support, hormonal therapy, and even in antibiotic therapy could contribute to longer survival today, even in the absence of potentially curative treatment. Nevertheless, these data provide outcome data for a cohort of patients infrequently encountered in the United States.

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